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| 10/828,395      | 04/19/2004  | John K. Jackson      | UBC.P-032           | 5836             |

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| EXAMINER |
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VIVLEMORE, TRACY ANN

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| ART UNIT | PAPER NUMBER |
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1635

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE  | DELIVERY MODE |
|--|------------|---------------|
| 3 MONTHS                               | 02/28/2007 | PAPER         |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

|                              |                               |                                |  |
|------------------------------|-------------------------------|--------------------------------|--|
| <b>Office Action Summary</b> | Application No.<br>10/828,395 | Applicant(s)<br>JACKSON ET AL. |  |
|                              | Examiner<br>Tracy Vivlemore   | Art Unit<br>1635               |  |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
  - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
  - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 23 October 2006.
- 2a) ☐ This action is **FINAL**.      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-15 is/are pending in the application.
- 4a) Of the above claim(s) 4,5,9,10,14 and 15 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-3,6-8 and 11-13 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)          | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

### DETAILED ACTION


In view of the appeal brief filed on October 23, 2006, PROSECUTION IS  
HEREBY REOPENED. New grounds of rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the  
following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply  
under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed  
by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and  
appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth  
in 37 CFR 41.20 have been increased since they were previously paid, then appellant  
must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by  
signing below:

  
JAMES SCHULTZ, PH.D.  
PRIMARY EXAMINER

The text of those sections of Title 35, U.S. Code not included in this action can  
be found in a prior Office action.

Any rejection not reiterated in this Action is withdrawn.

***Specification***

The disclosure is objected to because of the following informalities: the specification recites at page 4 that exemplary non-cancerous angiogenesis-related diseases are listed in table 1. It appears that this reference should be to table 4 because table 1 actually shows the results of experiments described in example 1.

Appropriate correction is required.

***Claim Objections***

Claim 11 is objected to because of the following informalities: the word "non-cancerous" is misspelled in line 2. Appropriate correction is required.

***Response to arguments: Claim Rejections - 35 USC § 112***

Claims 1, 6 and 11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. This rejection is maintained for the reasons set forth in the office action mailed December 27, 2005.

In the appeal brief of October 23, 2006, applicants argue the examiner is not looking at the question of whether the specification conveys to the person skilled in the art that the Applicants had possession of the invention as claimed, but rather whether they have provided an exhaustive list of examples including those that have not yet been invented. Applicants further argue the Federal Circuit has never said the written description requirement is intended to limit an applicant to the specific examples set forth in the application when the contribution to the art is greater in scope than those specific examples.

These arguments are not persuasive because the rejection discusses the working examples as part of summarizing what the specification describes, the rejection is not directed to any alleged lack of examples.

Applicants further argue the Examiner has not offered a reason why a person skilled in the art would not recognize in the description a disclosure of the full scope of the invention as claimed. This is not correct, the rejection describes why the disclosure is not commensurate with the claimed invention: the disclosure in the specification of antisense oligonucleotides or siRNA inhibitors does not lead the skilled artisan to the structures of other inhibitors of clusterin such as antibodies or small molecule inhibitors.

Applicants further argue the specification clearly conveys the inventors' understanding that the invention was broader than just the use of oligonucleotide therapeutics because the specification consistently refers to a "therapeutic agent" generically and specifically mentions the possibility of using an antibody to modify clusterin to an inactive form. However, a broad contemplation of therapeutic agents does not necessarily provide description of such agents. Adequate written description requires more than a mere statement that something is part of the invention.

Applicants argue the rejection does not focus on the invention as claimed, but on the therapeutic agent, and asserts that because the invention is a method for treating angiogenesis-related diseases and reducing angiogenesis by reducing the amount of clusterin, the test for compliance with the written description requirement should properly look at the invention to see if it fairly reflects the inventors' contribution to the art. Applicants appear to be overlooking the fact that the therapeutic agent is the central part of the invention, as it is the action of the agent that actually provides the

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therapeutic effect. Therefore, when the therapeutic agent is not described, the methods of the invention cannot be considered described.

Applicants assert the examiner is requiring applicant to test and discover every conceivable method for performing the methods of the invention. Applicants further assert the examiner "says that the claims must be limited to the genus of the specific examples" and that applicants are aware of no such burden imposed by the law of the United States. The rejection of record does not make any such requirements. The instant claims do not satisfy the written description requirement because the description of antisense oligonucleotides and siRNAs targeted to human clusterin provided by the specification does not describe a representative number of the genus of inhibitors encompassed by the claims. The structure of an antisense oligonucleotide does not lead the skilled artisan to the structure of any other type of inhibitor that has the function of inhibiting clusterin in all species. Applicants' arguments do not address the relationship of the structure of the disclosed inhibitors and the claimed function of inhibiting clusterin for the purpose of treating disease and thus do not overcome the rejection of record.

***New Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 6-8 and 11-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are directed to methods of reducing angiogenesis or treating a non-cancerous angiogenesis-related disease by reducing the amount of clusterin in an individual suffering from such a disease.

"Non-cancerous angiogenesis-related disease" is not a recognized term of art. The term "non-cancerous angiogenesis-associated diseases" is described at page 4 of the specification as referring to "non-cancerous diseases or conditions wherein inappropriate angiogenesis is observed as a symptom of the disease". It is assumed for the purposes of examination that this definition is also meant to serve for the term "non-cancerous angiogenesis-related disease".

The specification does not describe the nature of relationship to angiogenesis that is required in order for any particular disease to be an "angiogenesis-related disease". While the specification does state angiogenesis-related diseases exhibit "inappropriate angiogenesis", it is unknown whether "inappropriate" angiogenesis is limited to an undesired occurrence of angiogenesis or if a lack of angiogenesis can also be inappropriate, which would allow conditions resulting from lack of angiogenesis, such as ischemia, to be defined as "angiogenesis-related disease". Given the lack of definition of the term non-cancerous angiogenesis-related disease, the skilled artisan would be unable to recognize the metes and bounds of the claims because it is unknown what feature makes any particular disease angiogenesis-related. For example, table 4 lists dystrophic epidermolysis bullosa as one example of angiogenesis-

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related disease, but the teachings of the prior art regarding the role of angiogenesis in this disease is unclear. Arbiser et al. (Molecular medicine 1998, vol. 4, pages 191-195) suggest angiogenesis inhibitors as a treatment for dystrophic epidermolysis bullosa in order to antagonize basic fibroblast growth factor, which may contribute to the increased fibroblast collagenase observed in patients who have this disorder. However, Sibbald et al. (Ostomy Wound Management 2005, vol. 51, pages 22-46) teach that wound healing is essential for treatment of dystrophic epidermolysis bullosa and that angiogenesis encourages wound healing. While dystrophic epidermolysis bullosa might be considered an angiogenesis-related disease, it is not clear whether angiogenesis in this condition is "inappropriate" and therefore it is not clear that inhibition of angiogenesis would be a beneficial treatment for this condition.

The term "non-cancerous angiogenesis-related disease" is so broad as to encompass a supergenus of widely disparate conditions lacking a common etiology. The wide variety of conditions encompassed by the term "non-cancerous angiogenesis-related disease" are so disparate in terms of cause, patient population, presence of other symptoms and disease progression that it is unlikely the single act of reducing the effective amount of clusterin will be sufficient to provide a therapeutic treatment for all such conditions. Due to the immense breadth of the genus of conditions contemplated as being treatable by the instantly claimed method and the lack of clarity of the term, the metes and bounds of the claims are unknown and would not allow the skilled artisan to immediately recognize whether they are infringing the claims.

***Claim Rejections - 35 USC § 102***

The rejection over Monia et al. has been re-written below in order to clarify the grounds of rejection and the disclosure of the reference.

Claims 1, 2, 6, 7, 11 and 12 are rejected under 35 U.S.C. 102(b) as anticipated by Monia et al. (of record).

Claims 1 and 11 are directed to methods of treating a non-cancerous angiogenesis-related disease by administering to an individual suffering from the non-cancerous angiogenesis-related disease a composition that reduces the amount of clusterin in the individual. In claim 11 the individual is a human. Claim 6 is directed to a method of reducing angiogenesis in a non-cancerous angiogenesis-related disease by treating cells associated with the non-cancerous angiogenesis-related disease with a composition that reduces the amount of clusterin. Claims 2, 7 and 12 depend from claims 1, 6 and 11, respectively and recite that the therapeutic composition is an antisense oligonucleotide complementary to SEQ ID NO: 1.

Monia et al. disclose antisense oligonucleotides targeted to human clusterin and methods of using these oligonucleotides. One of these antisense oligonucleotides is designated as SEQ ID NO: 18, which is complementary to nucleotides 101-120 of instant SEQ ID NO: 1. At column 2, line 65 through column 3, line 6 Monia et al. disclose overexpression of clusterin is associated with atherosclerosis, a disease disclosed in the instant specification as being a non-cancerous angiogenesis-related disease. Monia et al. disclose at column 3, lines 40-46 a method of treating an animal,

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particularly a human, having a disease associated with expression of clusterin using the antisense oligonucleotides of their invention.

Claim 6 recites a method of reducing angiogenesis in cells associated with a non-cancerous angiogenesis-related disease by administering a composition effective to reduce the amount of clusterin in the cells. Monia et al. disclose antisense oligonucleotides that reduce the amount of clusterin and further disclose administering these oligonucleotides to an animal suffering from a disease associated with expression of clusterin. Monia et al. further disclose that atherosclerosis, a disease explicitly disclosed in the instant specification as an example of a non-cancerous angiogenesis-related disease, is one such disease associated with expression of clusterin. Therefore, although silent with regard to the ability of their method to reduce angiogenesis in a non-cancerous angiogenesis-related disease, because Monia et al. disclose administering a composition effective at reducing clusterin to the cells of an animal that is suffering from a non-cancerous angiogenesis-related disease and because performing this method would be treatment of cells associated with the disease, the method of Monia et al. would, absent evidence to the contrary, provide the recited effect of reducing the occurrence of angiogenesis.

Thus, Monia et al. disclose a method of inhibiting clusterin expression in disease-associated cells and individuals suffering from such diseases using an antisense oligonucleotide complementary to SEQ ID NO: 1 and anticipate claims 1, 2, 6, 7, 11 and 12.

***Response to arguments***

Applicants traverse the rejection over Monia et al. by arguing independent claims 1 and 11 are methods for treatment of a non-cancerous angiogenesis related disease and the examiner does not allege that Monia teaches treatment of a non-cancerous angiogenesis-related disease but only asserts that Monia discloses "a method of inhibiting clusterin expression in disease-associated cells and in individuals from such diseases." The rejection has been re-written to clarify the disclosure of Monia et al.

With regard to claim 6, applicants argue the statement in the rejection that the Monia reference "is silent with regard to inhibition of clusterin resulting in reduction of angiogenesis" indicates the examiner is either ignoring the reference to reduction of angiogenesis in the claim, or relying on some theory of inherency in support of this rejection and that neither is proper.

Applicants cite the decision in *Eaton Corp. v. Rockwell International Corp.* to support the argument that the reference to reduction of angiogenesis in claim 6 cannot be ignored. It is noted, however, that nothing in this decision precludes a finding of inherency.

Applicants' arguments regarding *Jansen* are unpersuasive because the facts are not analogous to the instant claims. In *Jansen* the cited art did not suggest use of the composition for use in treating macrocytic megaloblastic anemia. Monia et al., however, suggests treatment of diseases associated with clusterin overexpression and identifies atherosclerosis as such a disease. Therefore, Monia et al. suggest treatment of a disease that is an angiogenesis-related disease.

Applicants' arguments with regard to *Rapoport* are unpersuasive because the method of Monia et al. is intentionally disclosed as treating atherosclerosis, a disease defined in the instant specification as an angiogenesis related disease.

Applicants further argue that while the examiner has identified atherosclerosis as a condition identified in the present application as being an angiogenesis-related disease, it cannot be inferred from the reference that treatment of atherosclerosis using clusterin reduction would result in reduction in angiogenesis or that any therapeutic benefit that might flow from such a treatment would have anything to do with angiogenesis. Applicants further argue that in Monia, clusterin is identified as a circulating high density lipoprotein that is involved in cholesterol metabolism and that is a regulator of lipid transport and redistribution. Thus, Monia teaches a previously known activity in the context of atherosclerosis that has nothing to do with angiogenesis.

Applicants are correct that the examiner is relying on inherency to support the rejection of claims 6 and 7. It is noted that the instant specification explicitly recites in table 4 that one example of a non-cancerous angiogenesis-related disease treatable by the instantly claimed methods is atherosclerotic plaque growth and hemorrhage, a buildup of cholesterol and fatty material within a blood vessel due to the effects of atherosclerosis. Applicants' argument that one cannot infer that treatment of atherosclerosis using clusterin reduction would result in reduction in angiogenesis or that any therapeutic benefit that might flow from such a treatment would have anything to do with angiogenesis would appear to support an enablement rejection against claim 6.

Further, while Monia may have thought that a previously known activity of clusterin (e.g., regulation of lipid transport and redistribution) is providing the effect of treating atherosclerosis, this does not preclude an inherent anticipation of the instant claims. As stated in MPEP 2112, there is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of the invention, but only that the subject matter is in fact inherent in the prior art reference.

Monia et al. disclose antisense oligonucleotides targeted to clusterin and disclose administering a composition effective at reducing clusterin to the cells of an animal that is suffering from a non-cancerous angiogenesis-related disease. Therefore, because atherosclerosis is a non-cancerous angiogenesis-related disease and Monia et al. teach administering antisense oligonucleotides targeted to clusterin to animals suffering from this disease, which would be treatment of cells associated with the disease, and because it has since been discovered that inhibition of clusterin has the effect of reducing angiogenesis, the disclosure of Monia et al. anticipates the instant invention.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

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the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 6-8 and 11-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Monia et al. as applied to claims 1, 2, 6, 7, 11 and 12 above, and further in view of Gleave et al. (WO 00/49937, of record).

The claims are directed to methods of treating or reducing angiogenesis in a non-cancerous angiogenesis-related disease by administering a composition that reduces the amount of clusterin. In specific embodiments the therapeutic composition is an antisense oligonucleotide complementary to SEQ ID NO: 1 and the individual treated is a human. Claims 3, 8 and 13 recite that the antisense oligonucleotide is SEQ ID NO: 5.

The teachings of Monia et al. are described in the 102 rejection over this reference. Monia et al. do not teach the use of SEQ ID NO: 5 to inhibit clusterin.

Gleave et al. teach clusterin is a ubiquitous protein with a diverse range of proposed activities. Gleave et al. further teach inhibition of clusterin using antisense oligonucleotides for the purpose of treating prostate cancer. One of the antisense oligonucleotides targeted to clusterin, SEQ ID NO: 4, is identical to SEQ ID NO: 5 of the instant application. Gleave et al. teach in figure 3 and on page 7 that in prostate tumor cells SEQ ID NO: 4 provides the most effective downregulation of clusterin expression.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the antisense oligonucleotide designated as SEQ ID NO: 4 by Gleave et al. in the method of reducing clusterin expression in an animal suffering from a disease associated with clusterin expression such as atherosclerosis as taught by Monia et al. Monia et al. provide a motivation to use antisense oligonucleotides to treat diseases such as atherosclerosis that are associated with clusterin expression by explicitly suggesting such treatment while Gleave et al. provide a motivation and reasonable expectation of success in using the sequence designated as SEQ ID NO: 4 by teaching this antisense sequence is particularly effective in downregulating expression of clusterin.

Thus, the invention of claims 1-3, 6-8 and 11-13 would have been obvious, as a whole, at the time the invention was made.

### ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:45-5:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz, can be reached on 571-272-0763. The central FAX Number is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance.

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Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see <http://pair-direct.uspto.gov>.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Tracy Vivlemore  
Examiner  
Art Unit 1635

TV  
February 6, 2007

A handwritten signature in black ink, appearing to read 'R. Schnizer', with a stylized flourish at the end.

**RICHARD SCHNIZER, PH.D.**  
**PRIMARY EXAMINER**